# Volume homeostasis, renal function and hypertension

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## SUMMARY

*A generalised vasoconstriction, for almost a century believed to be the basis of all types of human hypertension, was disproved by recent haemodynamic studies. In our investigation of hypertension in chronic parenchymatous non-uraemic, non-anaemic renal disease, we have established that the earliest haemodynamic abnormality in subjects, of whom over 90% later develop high blood pressure, has actually started while their blood pressure is still normal. This consists of hypervolaemia and a high cardiac output (hyperkinesis) with tissue hyper-perfusion. Hypervolaemia is due to a failure of these still normotensive patients to excrete isotonic saline as readily as subjects with completely normal kidneys.*

*The chronic hypervolaemia in these subjects leads to a release of the natriuretic factor which depresses the $Na^+$-$K^+$-ATPase in the cell membranes and which is responsible for an increase in sodium (and calcium) content of the vascular smooth muscle cells, diminishing their compliance and thus raising the vascular resistance together with the thickening of the vascular wall of the originally hyperperfused vessels. With the disappearance of the vascular adjustment to the increased cardiac output, the blood pressure rises and the 'pressure diuresis' restores the circulating blood volume (and the renal homeostatic efficiency) to normal. With a further rise of the peripheral vascular resistance the cardiac output falls. At this late stage of renal hypertension renin may play a contributory role.*

*Thus, the primary abnormality in the chain of events leading eventually to hypertension is a renal inability to maintain a proper balance between sodium intake and output. This suggested pathophysiological mechanism is probably valid in every kind of human hypertension where a reason for such a disturbance is present.*

## INTRODUCTION

In his *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*, published 125 years ago, Claude Bernard[1] deduced with a clear foresight that a constancy of the 'milieu interne' is a prerequisite of the 'freedom and independent existence' of the body. Fifty years later, Starling[2] concluded that both the osmolality and the volume of the extracellular fluid belong to the constants regulated by the body within narrow limits. Whilst the former is homeostatically controlled by the hypothalmic osmoreceptors and the posterior pituitary lobe, and whilst the organism is protected against larger losses of the extracellular fluid which endanger the body by a hypovolaemic shock to the

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renin-angiotensin-aldosterone system, protection against isotonic volume expansion appears to be less alert.

Almost 50 years ago Smith[3] showed that ingestion of 1000 ml 1% salt solution in man will produce only a minimal (if any) diuretic response. In this respect, dogs respond faster, the renal reaction consisting of a rise of renal blood flow and glomerular filtration rate (GFR).[4]

## TWO TYPES OF HAEMODYNAMIC AND DIURETIC RESPONSE TO ISOTONIC VOLUME EXPANSION IN MAN.

Studying the haemodynamic, diuretic and humoral response to an intravenous saline infusion amounting to 2% body weight (bw), administered within 20 to 30 minutes to 61 fasting normotensive subjects recumbent at the time of the investigation, we have observed two types of haemodynamic behaviour.[5] In 31 the blood pressure remained completely unaffected by the isotonic fluid expansion (group A), whereas in 30 the blood pressure rose by some 14 mm Hg mean pressure (group B). Group B subjects were some 5 years older than those in group A but there was no difference between them in weight, height or sex distribution (Table). Group A consisted of 24 healthy subjects: four had a slight selective proteinuria below 1 g/24 hours without any other sign of a renal disease; in one, latent polycystic kidney disease without any restriction of renal function was discovered in the course of family screening and two gave a history of past border-line hypertension though blood pressure had been within the normal range without any drugs for several months. The mean 24 h glomerular filtration rate (GFR) of the whole group was $133 \pm$ SEM 11 ml/min and the difference between the mean GFR during day-time and night amounted to $28 \pm$ SEM 7 ml/min. Of the 30 subjects in group B, 29 had definite signs of a renal disease (glomerulonephritis bioptically confirmed in 13, interstitial nephropathy in 7, polycystic kidney disease in 2, mild vascular nephrosclerosis with a normal blood pressure at the time of the study in 7). Their mean GFR was also within the normal range ($126 \pm 11$ ml/min), but the difference between the day-time and nocturnal mean was reduced to $11 \pm 2, 5$ ml/min, which was significantly less than in the previous group.

The cumulative water and salt excretion during the 8 hours following the infusion amounted to 64% and 63% of the ingested load in group A and to 47% and 46% in group B (Fig 1). This points to a restriction of the volume homeostatic
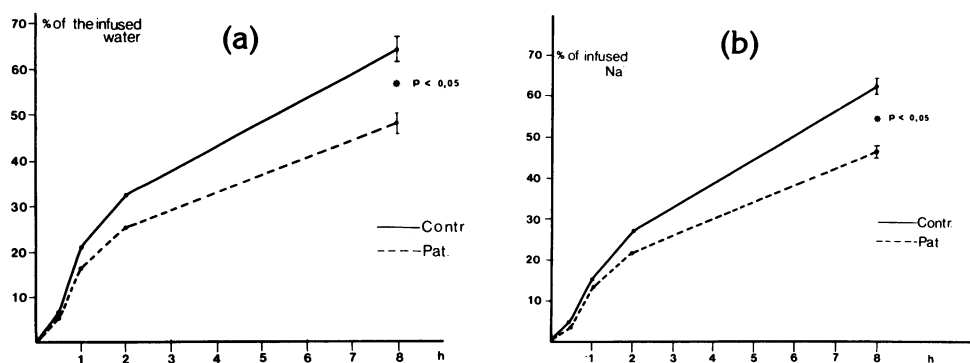


Fig. 1.　Cumulative excretion of (a) water and (b) sodium following an infusion of 20 ml/kg isotonic saline in 20·30 minutes to 18 perfectly healthy subjects (group A, Contr.). and to 10 subjects with minor renal pathology (group B — Pat.).

TABLE

Clinical and laboratory data on subjects in groups A and B

| | AGE | WEIGHT | HEIGHT | SEX | BLOOD PRESSURE | | MEAN BLOOD PRESSURE | | BLOOD VOLUME | HAEMATOCRIT | | PLASMA VOLUME | | GFR | span |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | years | kg | cm | m/f | mmHg | | mmHg | | ml/kg b.w. | | | ml/kg | | ml/min | day/night |
| | | | | | before | end of infusion | before | end of infusion | | before | end of infusion | before | end of infusion | mean | |
| **GROUP A** | | | | | | | | | | | | | | | |
| | 27.2 | 68.5 | 175.9 | 20/11 | 137/81 | 135/79 | 100.0 | 98.3 | 75.0 | 38.7 | 35.0 | 46.3 | 53.9 | 132.7 | 28.1 |
| SEM | ±1.25 | ±1.78 | ±1.63 | | ±3.5/3.0 | ±3.6/3.1 | ±2.9 | ±3.2 | ±10.9 | | | ±7.8 | ±9.0 | ±11.4 | ±7.1 |
| 31 | | | | | n.s. | | n.s. | | | <0.01 | | <0.01 | | | |
| **GROUP B** | | | | | | | | | | | | | | | |
| | 32.3 | 72.2 | 173.5 | 17/10 | 143/81 | 156/95 | 104.2 | 112.4 | 85.6 | 39.8 | 36.1 | 48.9 | 59.4 | 126.4 | 11.0 |
| SEM | ±1.67 | ±2.35 | ±1.87 | | ±4.6/3.6 | ±5.9/3.7 | ±3.7 | ±4.1 | ±13.3 | | | ±7.9 | ±10.2 | ±10.7 | ±2.5 |
| 30 | | | | | <0.01 | | <0.01 | | | <0.01 | | <0.01 | | | |
| A | <0.02 | n.s. | n.s. | n.s. | s <0.01 d <0.02 | | <0.02 | | <0.05 | n.s. | | n.s. | | n.s. | <0.05 |
| B | | n.s. | n.s. | n.s. | n.s. | | n.s. | | <0.05 | n.s. | | n.s. | | n.s. | |
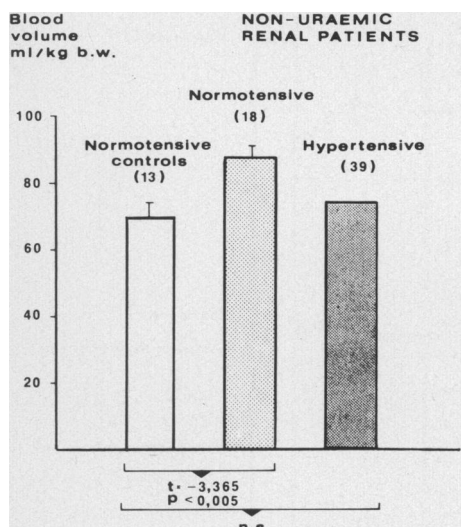
Fig. 2. Resting circulating blood volume in subjects of group A (normal) and group B (normotensive renal patients) and in hypertensive patients stage I to II WHO.

efficiency in group B with a possible trend to volume expansion. This was actually found.[5] The circulating basic blood volume (before the start of the infusion) in group A was $72 \pm 5$ ml/kg, and in group B $86 \pm 13$ ml/kg and the difference was statistically significant (Fig 2).

From the dilution of the plasma proteins at the time of the infusion it was possible to calculate that some 30% of the infused load was still within the vascular bed augmenting in both groups the circulating plasma volume. In 34 subjects (13 from group A, 21 from group B) in whom we have carried out detailed haemodynamic studies,[6, 7, 8] this raised the central venous pressure by some 125% and the cardiac output (CO) by some 25% in both groups (Fig 3). However, in group A there was a substantial drop of the total peripheral vascular resistance (TPR) from a control value of 1380 dyn.cm$^{-5}$ sec to less than 1000 dyn.cm$^{-5}$ sec at the end of the infusion whereas its fall was irregular and much smaller in group B. The forearm vascular resistance in group B was from the start significantly above that of group A and the forearm venous compliance rose markedly in group A, whilst it remained unchanged or fell in group B. Thus the two groups differed in their reaction of the peripheral vascular bed to the volume expansion: while it adjusted fully to the volume load in group A, it failed to adjust in group B.

*Atrial natriuretic factor.* The mechanism of this peripheral circulatory adjustment to the volume expansion in healthy subjects (group A) has been until recently only partially understood. Pressure-receptors in the heart atria were suspected and thought to mediate a reflex peripheral vasodilatation, slowing of the heart and a slight respiratory inhibition.[9, 10, 11] Recently, however, it has been possible to extract a group of polypeptides with a strong natriuretic and vasodilating action from the atria of rats (atrial natriuretic factor — ANF, atriopeptin). They appear to be produced or stored in the large secretory granula of the atrial cells (cardiocytes)[12] and are released on fluid expansion into the blood leaving the heart. Their presence has been established by radio-immunoassay, and their diuretic action is abolished by a specific antibody.[13-18] No proof of their existence in man has so far been reported, but, if confirmed, they would provide an adequate explanation of the augmented vascular compliance to an increased cardiac output and blood volume. The prompt rise of urine flow in rats contrasts with the slow onset of the diuresis on volume expansion in man and will require further study.
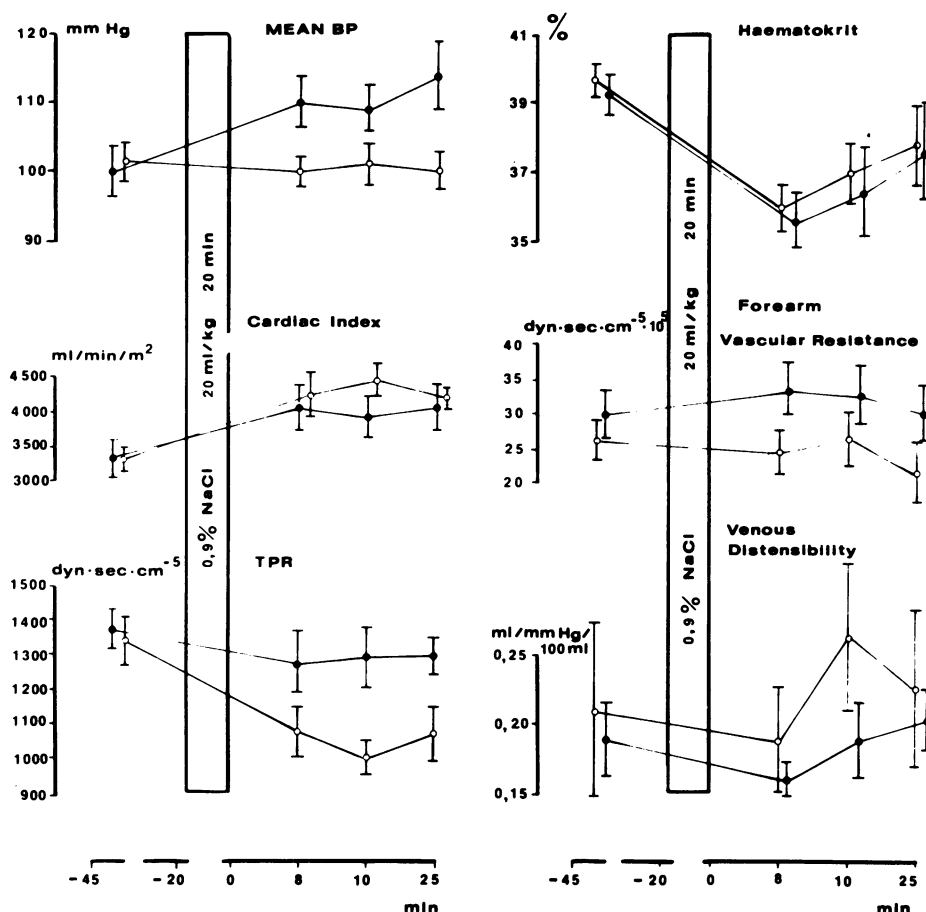
Fig. 3. Central and peripheral haemodynamic changes after volume expansion in 13 subjects in group A (open circles) and 21 subjects in group B (closed circles).[6]

$Na^+ \cdot K^+ \cdot cell \cdot membrane \cdot pump \cdot inhibiting$ natriuretic factor. This is of a so far uncertain biochemical nature, and is released on volume expansion from the hypothalamus in the neighbourhood of the anterior part of the third ventricle. It suppresses in an ouabain-like fashion the efficiency of the $Na^+ \cdot K^+$-pump in the cell membrane of the erythrocytes, leucocytes, vascular smooth muscle, heart muscle and possibly many other systems in the body with the result that these cells become depleted of potassium and richer in sodium.[19-22] In the kidney this leads to a diminished sodium reabsorption and an increased natriuresis. It has been postulated that the diminished membrane potential permits more calcium to enter the cells and that this is the reason for their diminished compliance, increased contractility and irritability.[23] This latter point is still controversial but the recent findings of an increased cytoplasmic calcium in the thrombocytes of spontaneously hypertensive rats and in essential hypertensive patients[24] lend support to this possibility.

Activation of this principle in normotensive men after volume expansion of some 3-4 litres of isotonic saline administered over several hours will lead to the

appearance of natriuretic activity.[25, 26] We have tested this question in our group A subjects before and after volume expansion as described above, studying the $^{42}$K-uptake from an isotonic saline solution with added $^{42}$K$^+$ with and without ouabain (the pump activity being the difference in $^{42}$K transport between the two). The intra-erythrocyte electrolyte concentration was also estimated.[27] In healthy subjects the $^{42}$K$^+$ transport into the erythrocytes amounted to $1.34 \pm 0.28$ mmol.h$^{-1}$.l$^{-1}$ RBC and the intra-erythrocyte sodium concentration to $6.14 \pm 1.86$ mmol.l$^{-1}$ RBC. At the end of the infusion in these healthy subjects the activity of the pump was unchanged (Fig 4). The meaning of this finding will become evident after the changes in group B have been discussed. The plasma renin activity (PRA) fell to insignificant levels after the infusion in all subjects.
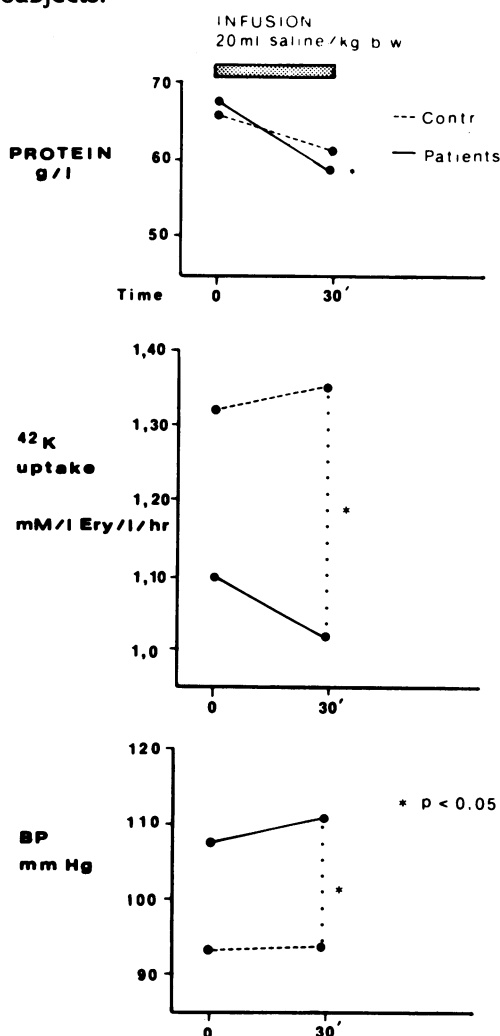


Fig. 4.   Changes of plasma protein concentration, $^{42}$K-uptake by the erythrocytes and blood pressure after volume expansion as in Fig 1 in 18 subjects of group A and 10 of group B.[5]

*Isotonic volume expansion with a rise of blood pressure (group B).*
The situation is substantially different in this group where the volume expansion starts from a volume of blood *a priori* raised. These patients had already before the beginning of the infusion, as a consequence of the hypervolaemia, suppressed their Na$^+$-K$^+$-pump to $1.10 \pm 0.2$ mmol K$^+$.h$^{-1}$.l$^{-1}$ RBC. The intra-erythrocyte sodium concentration did not change substantially after the 15-minute infusion, but the intra-erythrocyte potassium concentration was slightly reduced in group B. These changes probably reflect an enhanced activity of the natriuretic principle of hypothalamic origin.[22]

*Hyperkinetic circulation in the normotensive renal patients.*
In a larger series of 97 patients (Fig 5) with chronic parenchymatous renal disease (glomerulonephritis, interstitial nephropathy, polycystic kidney disease) without anaemia (Hb above 12.5 g/dl) and with an adequate renal function (mean 24 hr GFR over 50 ml/min), there were 32 with a normal blood pressure (BP = 145/95 mm Hg, mean BP 115 mm Hg). More than one-third of these had a cardiac index exceeding by more than 2 SD$\emptyset$ the mean of the healthy controls ($3.09 \pm 0.26$ l/m$^2$/min). In spite of their very high cardiac
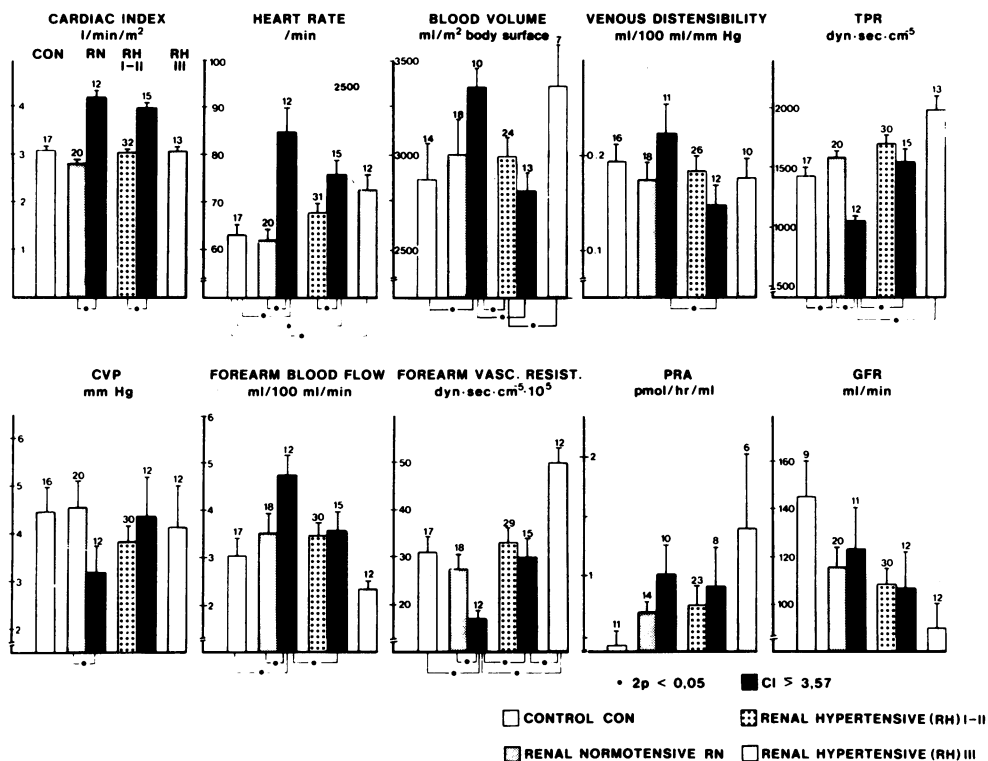
Fig. 5. Central and peripheral haemodynamic pattern, PRA and GFR in healthy controls (CON), in normotensive renal patients (RN) and in patients with chronic non-uraemic parenchymatous renal disease (RH I-II, RH-III) (WHO). The black columns indicate hyperkinetic subjects (cardiac index above 1.57 $1/m^2$ body surface). CVP = central venous pressure.

output (the mean cardiac index of these hyperkinetic subjects amounted to 4.18 $1/m^2/min$) these patients remained normotensive because both their TPR and the vascular resistance in their forearm were markedly diminished and adjusted to their high cardiac output. This resulted in an over-perfusion of tissues, evident from the strongly increased forearm blood flow (5 ml/100 ml forearm/min compared with 3 ml in controls). The venous compliance was also enhanced, adjusted for the very high circulating blood volume of 93 ml/kg. Fig 6 shows that 92 % of these subjects developed hypertension in the course of the following 2 to 6 years, compared with the 45 % of the normokinetic ones.[8]

## DEVELOPMENT OF RENAL HYPERTENSION

This transition is obviously ushered in by the loss of peripheral vascular adjustment: the TPR is now back at its control value, so is the forearm vascular resistance. When this happens, the kidney is perfused under an increased pressure, and possibly, with the contribution of the $Na^+$-$K^+$- inhibiting natriuretic principle whose activity has already been raised by the hypervolaemia of the normotensive stage (Fig 7),[27] regains its volume-homeostatic efficiency at a higher blood pressure level. This explains why in the past this 'transient variable' of hypervolaemia, present only in the normotensive renal patients, remained

undetected, as hypertensive renal patients were compared only with normotensive healthy controls.[28]

Renin and angiotensin can hardly be held responsible for this loss of peripheral adjustability, PRA being the same or even slightly lower (1.22 ng/ml/h) in these than in the normotensive renal patients (1.32 ng/ml/h) where the adjustability of the vessels had been fully preserved (Fig 5)[8] The occupation of the angiotensin vascular receptors by the inactive angiotensin antagonist saralasin did not reduce the blood pressure of these early renal hypertensive subjects (Fig 8).[29]

Further development of hypertension to stage III (WHO) now becomes entirely a function of the peripheral
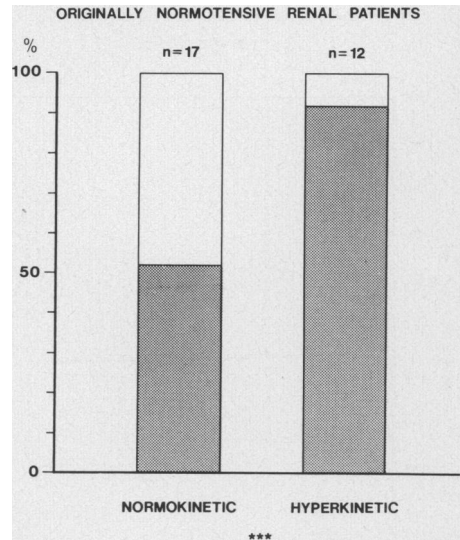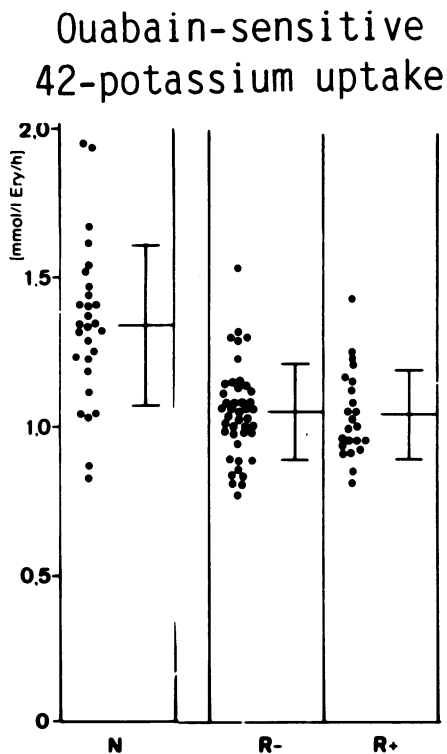
Fig. 6. Later incidence of hypertension in previously normotensive renal patients.

## Ouabain-sensitive 42-potassium uptake
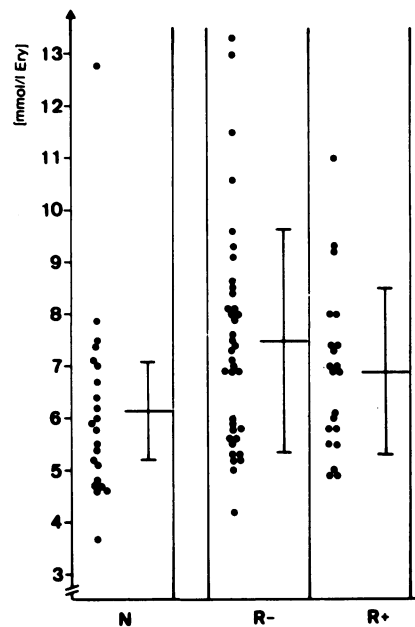
## Intracellular sodium concentration

Fig. 7. [42]K-uptake by the erythrocytes mmol/l RBC/h and sodium content of the erythrocytes mmol/l RBC in normotensive healthy controls (N) and in renal patients without (R −) and with (R +) hypertension.[27]

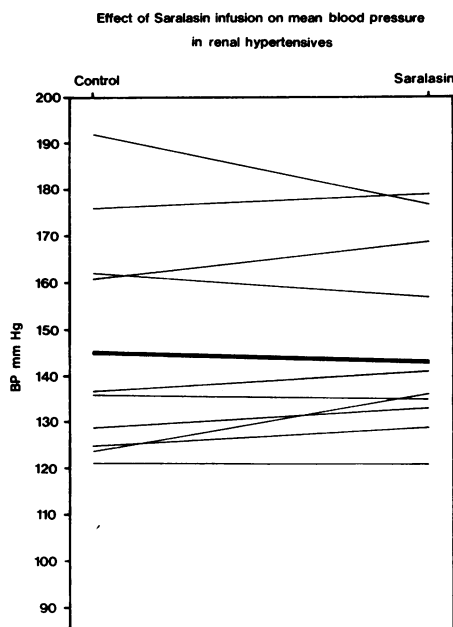Effect of Saralasin infusion on mean blood pressure
in renal hypertensives



Fig. 8. Effect of a graded one hour-lasting saralasin infusion on mean blood pressure in chronic renal hypertensive patients. Blood pressure fell slightly in only one subject with severe hypertension and elevated plasma renin activity (PRA).[29]

vessels whose ratio wall thickness/vessel lumen is unchanged or raised (Fig 9)[30, 31] and whose compliance is diminished (Fig 5), probably through the inhibition of the $Na^+$-$K^+$-pump in the smooth vascular muscles (Fig 7). With the increase of the TPR the cardiac output drops back to its original volume (reflexly?). At this late stage, we cannot rule out the possibility that the renin angiotensin system, whose activity is occasionally raised, may contribute to the development of the high TPR and of the malignant vascular changes,[32, 33] accelerating from now on the downhill course of the disease.

## DISCUSSION

The message contained in these studies can be summarised as follows. The haemodynamic alterations leading eventually to hypertension in chronic non-uraemic parenchymatous renal disease do not consist of a generalised vasoconstriction by an overproduction or deficiency of some vasoactive renal agent. Instead, there is a hypervolaemia, due—as shown by the sluggish excretion of the infused saline—to a disturbed renal volume homeostasis, with a subsequent rise in cardiac output and hyperperfusion of tissues. As long as the usual adaptation to this occurs, no change of blood pressure will be observable. Hypertension will develop when this peripheral adaptation is overruled — possibly by the thickening of the previously hyperperfused vessels and by an increased content of the smooth vascular muscles of sodium (and perhaps calcium) due to the inhibition of the $Na^+$-$K^+$-pump in the vessel wall by the ouabain-like natriuretic factor released by the initial hypervolaemia of the chronic renal disease.

A few critical words about the methods on which these important conclusions are based must be added. The cardiac output is the mean of at least three successive measurements at 5 to 10 minute intervals under resting conditions, and the difference between the individual data did not exceed 10%. The intra-individual confidence interval between single readings amounted to 8.3%. The error involved in the measurement of the circulating blood volume by the dilution of the [113]indium-labelled transferrin on repeated measurements in the same person was ± 5% and the values agree with those obtained with the ^{51}Cr-labelled erythrocytes. Uncertainty exists about the best reference basis. Whilst our isotope laboratory uses body *weight* for this purpose, it appears that body *height* may be more suitable.[28] We have therefore related our data to both the weight and body surface, the calculation of which includes both these parameters. The results with both these methods revealed the same significant difference between blood volume of the renal hyperkinetic normotensives and all the other subgroups. The slightly higher age (5 years) of group B can hardly be held responsible for a 20%
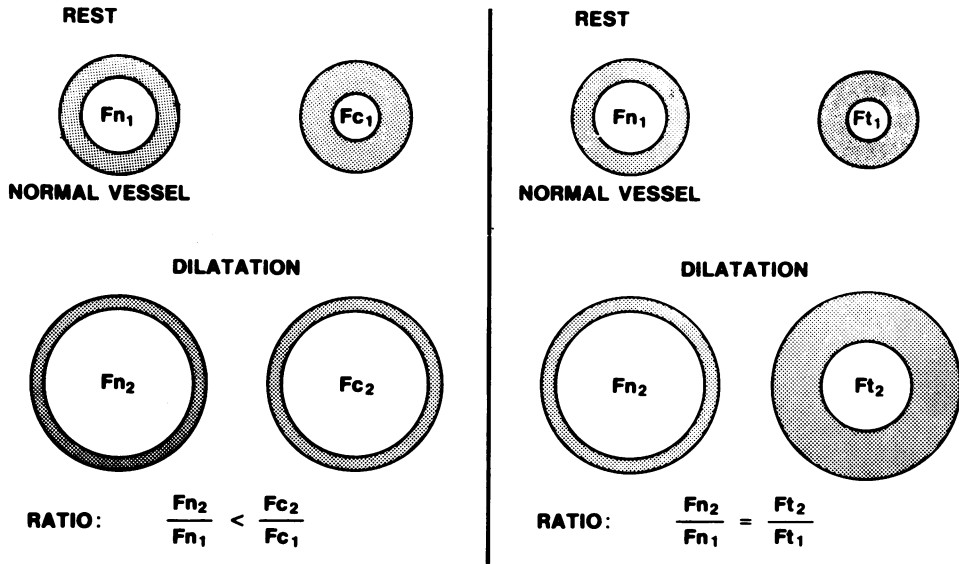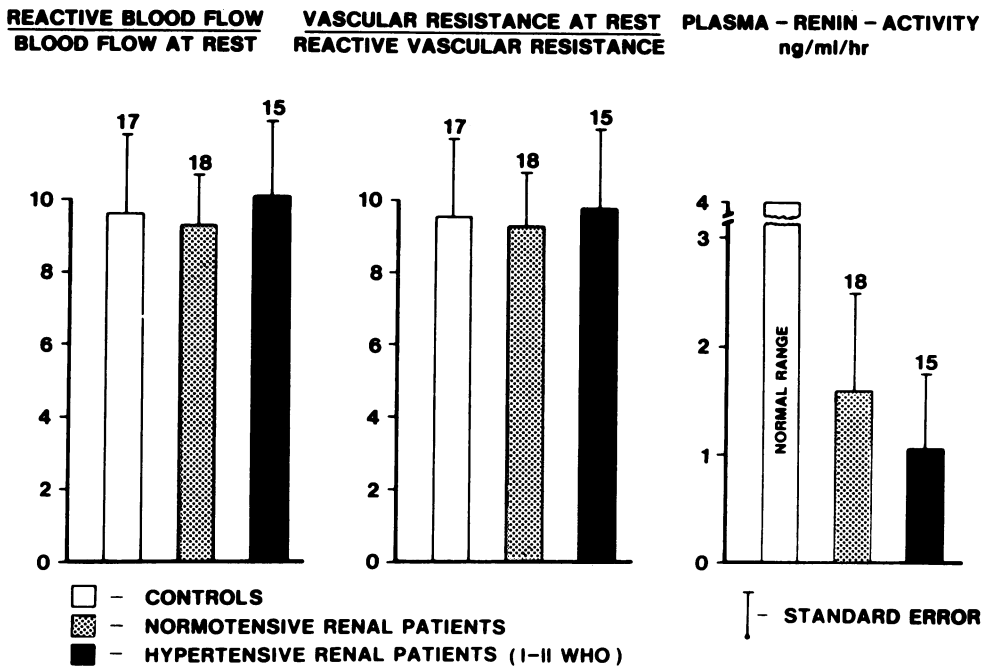
**REST**

$Fn_1$

NORMAL VESSEL

$Fc_1$

**DILATATION**

$Fn_2$

$Fc_2$

RATIO: $\dfrac{Fn_2}{Fn_1} < \dfrac{Fc_2}{Fc_1}$

**REST**

$Fn_1$

NORMAL VESSEL

$Ft_1$

**DILATATION**

$Fn_2$

$Ft_2$

RATIO: $\dfrac{Fn_2}{Fn_1} = \dfrac{Ft_2}{Ft_1}$

## I. ACTIVE VASOCONSTRICTION    II. VESSEL HYPERTROPHY

**REACTIVE BLOOD FLOW** / **BLOOD FLOW AT REST**

**VASCULAR RESISTANCE AT REST** / **REACTIVE VASCULAR RESISTANCE**

**PLASMA – RENIN – ACTIVITY** ng/ml/hr

□ – CONTROLS
▨ – NORMOTENSIVE RENAL PATIENTS
■ – HYPERTENSIVE RENAL PATIENTS (I–II WHO)

⊥ – STANDARD ERROR

Fig. 9. The ratio 'maximum hyperaemic' to resting forearm blood flow, forearm vascular resistance and plasma renin activity (PRA). A vessel can dilate on the removal of all vasoconstrictor influences only to a given maximum. Hence a constricted vessel will dilate on producing maximum hyperaemia (combination of indirect heating with reactive hyperaemia) more than a previously unconstricted vessel and the ratio maximum flow/resting flow after the removal of vasoconstriction will increase more than with a previously unconstricted vessel.

difference in the cardiac output between groups A and B. We thus could see no other reason why the hypervolaemia and hyperkinesis should be restricted to the normotensive renal patients than that these two changes are the first steps in the development of the haemodynamic abnormality of chronic renal disease leading eventually to hypertension, being analogous to the changes produced by isotonic volume expansion in normotensive subjects with a slight renal defect.

Whereas in healthy normotensive subjects on mild to moderate volume expansion a mechanism analogous to the ANF in rats produces increasing vascular compliance and urine flow, a larger fluid expansion, or a fluid expansion superimposed on a volume of blood *a priori* raised, as in normotensive subjects with a renal defect, will activate the $Na^+ \cdot K^+$-pump inhibiting factor. Whether by this time the vasodilating activity is already exhausted by the protracted hypervolaemia, as suggested by the depletion of the secretory granules in the cardiocytes on volume expansion in rats,[34] or whether in the competition of these two activities (which obviously differ in the mechanism of their action), the ouabain-like factor gains the upper hand, is a matter for further study. Perhaps the sodium- and calcium-loaded vascular smooth muscle cells cannot respond any more to the vasodilating principle.

The ways by which renal disease interferes with the volume homeostatic efficiency of the kidney have still to be explored. Although the GFR of many of the investigated patients was within the normal range, the day and night span of the GFR was reduced in group B, suggesting that the adaptation of this renal function to the exigencies of the volume homeostasis may be restricted. Knowledge of the effect of the various renal parenchymatous diseases on the various intrarenal natriuretic humoral factors, such as the prostaglandins, dopamine[35] or kallikrein, is inadequate. On the other hand it is certain that many other conditions causing hypertension, such as primary aldosteronism (Conn's syndrome), renal artery stenosis or constriction, and intrarenal vasoconstriction, interfere with normal sodium excretion and thus with volume homeostasis.

In essential hypertension there are several possibilities, corresponding perhaps to different etiologies of the disease. There are many indications that the autonomic equilibrium is out of balance, with a 'sympathetic overdrive' starting when the subject was no more than 20 to 30 years of age.[36-40] The consequence is an exaggerated reaction to simple blood pressure-raising stimuli (pain, rage, anxiety) which in the kidney leads to a protracted exaggerated vasoconstriction. The previous reaction may actually merge with the next one and eventually may be present for most of the day, leading to positive water and salt balance. As the sympathetic overactivity may stop during quiet night sleep, the renal vaso-constriction will subside explaining the nocturia of these early essential hyper-tensives, present in some 60% of cases.[41, 42] There are also age-dependent changes in the kidneys which may be the basis of the blood pressure rise with age,[43] such as the progressive thickening of the glomerular basement membrane with age in rats.[44] Whether this has an analogy in man is so far unknown. The genetic element may have something to do with the renal natriuretic cascade which is still a wide field for investigation.

Thus even a slight restriction of renal function may reduce volume homeostatic efficiency and raise blood pressure. This will re-establish volume homeostasis at a higher blood pressure level. However, the organism has to pay a high price for this compensation by an increased risk of cardiovascular complications which may prove fatal.

# APPENDIX

## *Methods used*

| | |
|---|---|
| Blood pressure | strain gauge, catheter in the femoral artery. |
| Cardiac output | Indocyanine green dilution, arterial blood drawn from femoral artery. |

Total peripheral vascular resistance (TPR)

$$\frac{\text{mean BP (electronically integrated)}}{\text{cardiac output}/60} \times 1332 \text{ dyn.cm}^{-5} \text{ sec.}$$

| | |
|---|---|
| Forearm blood flow | Whitney occlusion plethysmograph. |

Forearm vascular resist.

$$\frac{\text{mean blood pressure}}{\text{forearm blood flow}/60} \times 1332 \times 10^{-5}$$

Forearm blood volume

$^{113}$indium-transferrin dilution in the forearm ½ hour after its injection by a central catheter is quantitatively calibrated by the increase in both volume ($\triangle$ V) (measured plethysmographically) and radioactivity ($\triangle$ A) : $\dfrac{\triangle A}{\triangle V} = \dfrac{A}{V}$

| | |
|---|---|
| Venous distensibility (compliance) | Forearm blood volume/forearm venous pressure |
| Central venous pressure | Catheter in superior vena cava close to the atrium. |
| Plasma renin activity (PRA) | Isotope double dilution technique. |
| Glomerular filtration rate (GFR) | Mean of the endogenous creatinine clearance for two 12-hour periods. |

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